Integrative network-based approaches for modeling human disease

Chapter 8

Valorization

The multifactorial nature of neurodevelopmental disorders, like Batten disease, or age-related disorders, such as Alzheimer's disease (AD), requires the generation and integrative analysis of biological data from different regulatory levels (genomics, epigenomics, and transcriptomics) to advance our understanding of the underlying mechanisms. A deep and thorough understanding of these multi-layered mechanisms at systems-level is the key to deconvolute the complexity of human pathologies, hence fostering the development of novel and effective treatment strategies.

Despite recent advances in next-generation sequencing technologies and the development of novel computational modeling approaches that shed more light on disease processes, we are still far from completely characterizing the disease-causative agents and finding a definite cure for most human pathologies, including AD. This highlights the need for explorative studies that utilize multi-level regulatory information to decipher the underlying mechanisms controlling normal gene expression regulation and their dysregulation in human disorders. In order to meet this challenge, the research presented in this thesis aims to further accelerate research in the field of computational disease modeling. Though it is unlikely that the work carried out in this thesis will have a direct impact on society in the short run, the approaches introduced here will definitely guide future studies, bringing the existing knowledge one step closer to its applications in disease intervention.

All in all, the research presented in this thesis highlights the potential of computational disease modeling and integrative multi-omics analysis for dissecting human disorders and proposing ra-

tional therapeutic strategies. For example, the approach presented in chapter 3 may find its application in facilitating experimental attempts for treating human developmental disorders, that arise due to a disruption in the normal cellular differentiation process [161, 295]. To this end, the proposed method (INTREGNET) is able to predict specific sets of instructive factors (IFs) that can induce desired cellular conversion events with increased efficiency, hence overcoming a long-standing problem in regenerative medicine hampering the translation of therapeutic interventions into clinical applications.

The research work described in chapters 4 and 5, focused on AD, offers novel insights into epigenetic and transcriptomic dysregulation by comparing multi-omics datasets from patients and healthy controls. Different markers identified at the genome-wide level, as well as by zooming in on sphingolipid metabolism, can be further tested for their potential as diagnostic markers or as putative drug targets. Furthermore, expanding existing knowledge about the involvement of different regulatory layers in AD-associated dysregulation is already a merit on itself, as such a deeper understanding of underlying mechanisms is vital for the development of novel therapeutic intervention strategies.

The final scientific efforts described in chapter 6 are directed towards generating a computational model of Batten disease in order to understand the functional consequences of a particular mutation in the *CLN3* gene, and to identify genes and pathways compromised in this human neurodevelopmental disorder. The conducted gene regulatory network (GRN) and *in-silico* gene perturbation analyses revealed key driver genes in maintaining the diseased phenotype network, i.e. leading to a significant reversion of the pathological gene expression program upon perturbation. The reported findings not only highlight the potential of employed systems-level approaches to identify relevant genes and associated molecular mechanisms implicated in Batten disease, but also provide a prediction of putative candidate genes that might be the drivers of disease-related dysregulation. We believe this study has a direct impact on the society as it provides the scientific community with a very a first *in vitro* and *in silico* *CLN3*^{Q352X} mutation Batten disease model, as well as the fact that it identifies key genes to be experimentally validated for their potential as an early diagnostic marker or target for designing potential therapeutic treatment strategies.

Taken together, the research work conducted in this thesis may have a substantial impact on our society, providing the scientific community with novel approaches to develop computational disease

models and dissect their underlying mechanisms. These computational models can help us unlock the biological systems [29], as well as devise new intervention strategies to halt the progression of human disorders or cure them. Finally, after going through four years of extensive training and hands-on practical experience, I am confident in saying that my efforts have allowed me to explore the computational disease modeling field in depth, also identify associated gaps and weaknesses in existing knowledge and approaches. During the last year of my project, I have stretched my skills beyond the vigorous foundation provided by my supervisors to meet the requirements to advance in this field. The expertise I have gained throughout my Ph.D. trajectory has enabled me to design my own studies and write grant proposals, which means I am now ready to make a real impact on society as an independent researcher.